

PATENT COOPERATION TREA



10/540086

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicar 	nt's or agent's file reference	FOR FURTHER ACTIO	N See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)
	onal application No. I 03/00302	International filing date (dayling 09.09.2003	onthlyear) Priority date (day/monthlyear) 18.12.2002
Internation C12Q1		or both national classification and IPC	
Applican			
DEPAF	RTMENT OF BIOTECHNO		
1. Th Au	is international preliminary e	xamination report has been prep the applicant according to Article	ared by this International Proliminary Function
2. Thi	is REPORT consists of a tot	al of 7 sheets, including this cove	er sheet.
⋈	occir arrierided and are tr	panied by ANNEXES, i.e. sheets be basis for this report and/or she ion 607 of the Administrative Inst	of the description, claims and/or drawings which have ets containing rectifications made before this Authority ructions under the PCT).
The	ese annexes consist of a total	of 10 sheets.	
******************	·		er en
3. This	report contains indications	relating to the following items:	
ı	Basis of the opinion		
11	☐ Priority		
Ш	Non-establishment o	f opinion with regard to novelty, in	nventive step and industrial applicability
IV	Lack of unity of inver		,
V	Reasoned statement citations and explana	under Rule 66.2(a)(ii) with regard tions supporting such statement	d to novelty, inventive step or industrial applicability;
VI	☐ Certain documents c	ted	
VII	Certain defects in the	international application	
VIII	☐ Certain observations	on the international application	
ate of sub	nission of the demand		completion of this report
		July 5.1	completion of this report
2.07.2004		22.02.2	2005
me and meliminary e	nailing address of the internation	al Authorize	ed Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 eprnu d		1	• • • • • • • • • • • • • • • • • • •
	Fax: +49 89 2399 - 4465	Telephon	ne No. +49 89 2399-7351

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/IN 03/00302

I. B	asis	of	the	rep	ort
------	------	----	-----	-----	-----

1. With regard to the **elements** of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):

	D	escription, Pages						
	1,	2, 4-10, 12-16, 19-2	4, 26-32	as published				
	3,	11, 17, 18, 25, 25a		received on 22.12.2004 with letter of 17.12.2004				
	Claims, Numbers							
	1-21			received on 22.12.2004 with letter of 17.12.2004				
	Dr	awings, Sheets						
	1.6	S-6 <i>f</i> 6		as published				
2.	With regard to the language, all the elements marked above were available or furnished to this Authority in language in which the international application was filed, unless otherwise indicated under this item.							
	Th	ese elements were a	vailable o	r furnished to this Authority in the following language: , which is:				
		the language of a to	ranslation	furnished for the purposes of the international search (under Rule 23.1(b)).				
		the language of pul	publication of the international application (under Rule 48.3(b)).					
		the language of a tr Rule 55.2 and/or 55	ranslation 5.3).	furnished for the purposes of international preliminary examination (under				
3.	Wit inte	th regard to any nucl ernational preliminary	eotide ar examina	nd/or amino acid sequence disclosed in the international application, the tion was carried out on the basis of the sequence listing:				
	\boxtimes	contained in the inte	ernational	application in written form.				
		filed together with th	ne interna	tional application in computer readable form.				
		furnished subseque	ntly to this	s Authority in written form.				
		furnished subseque	ntly to this	s Authority in computer readable form.				
		The statement that in the international a	the subse application	quently furnished written sequence listing does not go beyond the disclosure as filed has been furnished.				
		The statement that the listing has been furn	the informished.	ation recorded in computer readable form is identical to the written sequence				
	The	amendments have r	esulted in	the cancellation of:				
		the description,	pages:					
		the claims,	Nos.:					
		the drawings,	sheets:					

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/IN 03/00302

5. 🖾	This report has been established as if (some of) the amendments had not been made, since they have
	been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

- 6. Additional observations, if necessary:
- III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1.	The obv	e questions whether the claimed invention appears to be novel, to involve an inventive step (to be non- vious), or to be industrially applicable have not been examined in respect of:
		the entire international application,
	\boxtimes	claims Nos. 21
		because:
		the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
		the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
		the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
	\boxtimes	no international search report has been established for the said claims Nos. 21
2.	or a	eaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and mino acid sequence listing to comply with the standard provided for in Annex C of the Administrative ructions:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

the computer readable form has not been furnished or does not comply with the Standard.

the written form has not been furnished or does not comply with the Standard.

1. Statement

Novelty (N)	Claims Claims	1-20
Inventive step (IS)	 Claims Claims	1-20
Industrial applicability (IA)	 Claims Claims	1-20

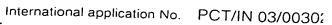
2. Citations and explanations

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/IN 03/00302

see separate sheet



Amendments

Two amended pages of sequences listing were filed with the letter dated 17.12.2004. A first page, denoted page 25, is listing 3 different sequences which correspond to a protein sequence of 16 amino-acids and two nucleic acid sequences of 645 and 618 nucleotides, respectively.

An second page, without page number, is listing two oligonucleotides identified by SEQ ID NO: 9 and SEQ ID NO:10. This page is denoted page 25a by the International Examination Authority.

Page 25 is considered by this Authority as not fulfilling the requirements of Rule 70.2(c) PCT.

Due to the use of the expressions "Seq id no. 6 (change to 8)", "Seq id no. 7 (change to 6)" and "Seq id no. 8 (change to 7)", the sequences listed on page 25 are not clearly and unambiguously identified by a sequence name (i.e. SEQ ID NO). Therefore, in the absence of a clear and unambiguous SEQ ID NO. for each of the three sequences listed on page 25, said page is considered as introducing subject-matter which goes beyond the application as originally filed.

The present report has been established as if the amendments on page 25 had not been made.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 21 was not searched (see PCT/ISA/210). Said claim is therefore not further examined (Article 34(4)(I)(ii), Article 17(2)(a) and Rule 66.1(e) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application relates to the hupB gene encoding a mycobacterial histone like protein, oligonucleotide primers to amplify the hupB gene and to a method for differentiating *Mycobacterium tuberculosis* from *Mycobacterium bovi*s.

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

Reference is made to the following documents:

D1: Prabhakar et al., "Identification of an immunogenic histone-like protein (HLPMt) of Mycobacterium tuberculosis.".

Tubercle and lung disease, 1998, 79, pages 43-53.

An abstract of said document has been cited in the International Search Report.

A copy of the original document is annexed to the present communication.

D2: Cohavy et al., "Identification of a novel mycobacterial histone H1 homolog (HupB) as n antigenic target of pANXA monoclonal antibody and serum immunoglobulin A from patients with Crohn's disease.",

Infection and immunity, 1999, 67, pages 6510-6517.

D3: WO99/45955, published 16 September 1999.

V.1. Novelty and inventive step of product claim 1.

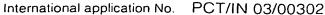
Document D1 discloses (the reference in parentheses applying to this document) the identification and cloning of the hupB gene of M. tuberculosis (abstract and Fig. 4B). Said document also discloses two oligonucleotide primers to amplify said hupB gene which are different from the primers of Seq ID Nos 1-5 of the present application (page 45, col.2, section "PCR analysis and sequencing).

Claim 1 is therefore new in the sense of Article 33(2) PCT.

The applicant has shown that a pair of primers selected from the group consisting of Seq ID No. 1-5 has a surprising effect over primers HLPMNdel and HLPMSall disclosed in document D1. A pair of primers selected from the group consisting of Seq ID No. 1-5 enables the differentiation between M. tuberculosis and M. bovis. Since, this effect is not suggested by document D1, it is considered surprising over the prior art.

Claim 1 appears, therefore, to involve an inventive step in the sense of Article 33(3) PCT.

V.2. Novelty and inventive step of method claims 2-20.



None of the prior art document at hand discloses nor suggests that M. tuberculosis and M. bovis can be differentiated based on the hupB gene.

Therefore, a method for differentiating M. tuberculosis and M.bovis by amplifying a part of the hupB gene with a pair of primers selected from the group consisting of Seq ID No. 1, Seq ID No. 2, Seq ID No.3, Seq ID No. 4 and Seq ID No. 5, detecting the amplified fragment and differentiating M. tuberculosis from M. bovis based on the size of the amplified fragment appear to be new and inventive.

Thus, claims 2-20 appear to be new in the sense of Article 33(2) PCT and to involve an inventive step in the sense of Article 33(3) PCT.

Further remarks.

1. Independent claim 2 is considered to lack clarity in the sense of Article 6 PCT due its wording.

Claim 2 relates to a method for differentiating Mycobacterium species. From the steps defining the method of claim 2, claim 2 is defining a method for differentiating M. tuberculosis and M. bovis rather than a method for differentiating Mycobacterium species.

2. The expression "method according to claim 2, said Mycobacterium species" used in claim 3 is unclear thereby rendering the scope of said claims unclear in the sense of Article 6 PCT. Said expression appears unclear as it seems that a word (i.e. wherein) is missing.

We Claim:

- 1. A pair of oligonucleotide primers for specific amplification of the hupB gene of Mycobacterium species selected from the group consisting of Seq ID Nos. 1 and 2; Seq ID No. 3 and 4; Seq ID No. 4 and 5.
- 2. A method for differentiating *Mycobacterium* species based on target *hup*B gene encoding for histone like proteins comprising steps of:
 - a) Obtaining DNA from culture or from clinical samples.
 - b) Amplifying a part of the target gene encoding for histone likeproteins such as hup B of Mycobacterium species using said DNA as a template in a polymerase chain reaction with a pair of oligonucleotide primers according to claim 1.
 - c) Detecting said amplified fragment of the hup B gene for the presence of M. tuberculosis and M. bovis and to differentiate Mycobacterium tuberculosis from Mycobacterium bovis based on the size of the amplified fragment.
- 3. A method according to claim 2, said *Mycobacterium* species is selected. from the group consisting of *M. tuberculosis* and *M. bovis*.
- 4. A method according to claim 2, wherein the pair of oligonucleotide primers comprises of Seq ID No. 1 and Seq ID No. 2.
- 5. A method according to claim 2, wherein the pair of oligonucleotide primers comprises of Seq ID No. 3 and Seq ID No. 2.
- A method according to claim 2, wherein the pair of oligonucleotide primers comprises of Seq ID No. 4 and Seq ID No. 5.



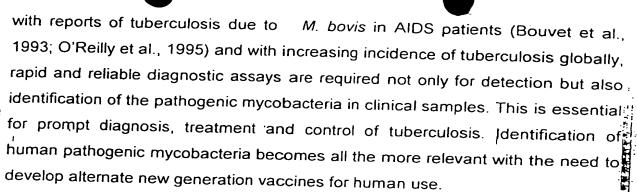
- A method of claim 2, wherein in step (c) the amplified fragments are detected by ethidium bromide staining or DNA probe hybridization.
- 8. A method as claimed in claim 2, wherein the step of differentiating comprising the steps of:
 - a) Designing a set of primers according to claim 1, Seq ID No. 1, Seq ID No. 2, Seq ID No. 3, Seq ID No. 4, Seq ID No. 5, to amplify a part of the said hup B gene from Mycobacterium tuberculosis and Mycobacterium bovis.
 - b) Obtaining DNA from culture or from clinical samples.
 - c) Amplifying a part of the target gene encoding for histone like proteins such as hup B of Mycobacterium species using said DNA as a template in a polymerase chain reaction with a pair of oligonucleotide primers according to claim 1.
 - d) Analyzing and validating the size of the amplified fragments.
 - e) Determining the complete Sequence of the said amplified fragments.
 - f) Inferring from the sequence whether it is M. tuberculosis or M. bovis.
- 9. A method according to claim 7 wherein the DNA probe consists of sequence ID No. 6 or sequence ID No. 7 or a complement thereof tagged with a detectable label.
 - 10. A method as claimed in claim 2 wherein the step of differentiation consists in determining the smaller size of the amplified fragment obtained from *Mycobacterium bovis*.
 - 11. A method according to claim 4 wherein the PCR amplified fragment in Mycobacterium bovis was 618 bp.
 - 12. A method according to claim 4 wherein the PCR amplified fragment in *Mycobacterium tuberculosis* was 645 bp.



- 13. A method according to claim 5 wherein the PCR amplified fragment in Mycobacterium bovis was 291 bp.
- 14. A method according to <u>claim 5</u> wherein the PCR amplified fragment in Mycobacterium tuberculosis was 318 bp.
- 15. A method according to <u>claim 6</u> wherein the PCR amplified fragment in Mycobacterium bovis was 89 bp.
- 16. A method according to <u>claim 6</u> wherein the PCR amplified fragment in *Mycobacterium tuberculosis* was 116bp.
- 17. A method according to claim 2 wherein the PCR amplified fragment in *Mycobacterium bovis* was 27 bp smaller than that of *Mycobacterium tuberculosis*.
- 18. A method as claimed in 2 wherein differentiating *M. tuberculosis* and *M. bovis* comprising the steps of :
 - a) Amplifying a part of the target hup B gene from M. tuberculosis and M. bovis in a polymerase chain reaction with primers Seq. ID No.1 and Seq. ID No.2
 - b) Restricting the amplified fragment with *Hpa II* restriction enzyme to produce restricted fragments.
 - c) Separating the restricted fragments by electrophoresis on 12% polyacrylamide gel
 - d) Detecting the restricted fragments by staining with ethidium bromide.
- A method according to claim 18 wherein the restricted fragment in M.;
 tuberculosis was 280 bp and 150 bp.
- A method according to claim 18 wherein the restricted fragment in M. bovis was 253 bp and 150 bp.

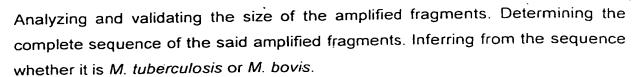
Page No. 36

A process as in preceding claims substantially as herein described.



Immunogenecity of HupB protein: Two methods were used to identify mycobacterial constituents associated with human response namely the T cell blot and immuno – subtraction assays (Prabhakar et al., 1998). The 30kDa fraction of the mycobacterial lysate was found to induce the highest lymphoproliferative index among the tuberculin reactors. In immuno-subtractive assays a prominent reactive band was similarly seen at approximately 30kDa. The 30kDa protein was electro-eluted from the SDS-PAGE gel and purified to homogeneity.

Using the internal peptide sequence, <u>Seq ID No. 8</u> (VKPTSVPAFRPGAQFK) a 100% identity was obtained with 16 amino acids of the cosmid CY349. The corresponding gene was later annotated and designated as the *hupB* gene (Rv 2986c, Cole et al., 1998). The protein was found to be localized in the cytoplasm and on the cytoplasmic surface of the mycobacterial membrane, by immuno-gold electron microscopy. The *hupB* gene has been classified among the DNA binding (histone like) proteins of *M. tuberculosis* (Cole et al., 1998). Primers were designed to amplify the *hupB* gene. A 645 bp amplicon was obtained in case of *M. tuberculosis*. The α^{32} P labeled PCR amplicon was used in Southern hybridization to establish the size, prevalence and organization of the *hupB* gene in members of the MTB complex (*M. tuberculosis* and *M. bovis*) and other mycobacterial species.



Another embodiment is a method wherein the DNA probe consists of sequence ID No. 6 or sequence ID No. 7 or a complement thereof tagged with a detectable label.

Another embodiment is a method wherein the step of differentiation consists in determining the smaller size of the amplified fragment obtained from Mycobacterium bovis.

Another embodiment is a method wherein the PCR amplified fragment in Mycobacterium bovis was 618 bp.

Another embodiment is a method wherein the PCR amplified fragment in *Mycobacterium tuberculosis* was 645 bp.

Another embodiment is a method wherein the PCR amplified fragment in Mycobacterium bovis was 291 bp.

Another embodiment is a method wherein the PCR amplified fragment in Mycobacterium tuberculosis was 318 bp.

Another embodiment is a method wherein the PCR amplified fragment in *Mycobacterium bovis* was 89 bp

Page No.17



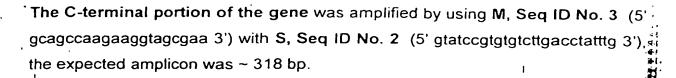
All the mycobacterial and non-mycobacterial strains grown on solid media (LJ slants all mycobacterial species), LB agar (*E. coli*) nutrient agar (*Aspergilus niger*, *Nocardia asteriodes*, *Pseudomonas aeruoginosa*, *Klebsiella pneumoniae*) or blood agar (*Corynebacterium diphtheriae*, *Streptococcus pneumoniae*) were scraped with the help of sterile toothpicks and re-suspended in sterile distilled water containing 0.1% Triton X-100. Re-suspended bacilli were boiled at 100°C for 20 minutes and an aliquot (2µI) was used for PCR.

PCR Analysis:

- 1) 23S rDNA target: Primers: C, Seq ID No.9(5' gtgagcgacgggatttgcctat 3') and L, Seq ID No. 10(5' accacccaaaaccggatcgat 3') were used to detect the presence of DNA from organisms belonging to genus Mycobacterium. The expected size of the amplicon was 174bp (Verma et al., 1994; Dasgupta et al., 1998).
- 2) hupB DNA **Primers** (5' target N. Seq ID No ggagggttgggatgaacaaagcag 3') and S. Seq ID No. (5': gtatccgtgtgtcttgacctatttg 3') were used to amplify hupB gene sequences. The expected size of the amplicon was ~645 bp (Table II, Fig:1) in M. tuberculosis and 618 bp in M. bovis.

Each reaction (20μl) contained 1.5 mM MgCl₂, 0.5 μM of primers, 200 μM dNTPs, 10 mM Tris-HCl (pH 8.8 at 25°C), 50 mM KCl, 0.08% Nonidet P40, and 0.5 Units of Taq DNA Polymerase. The PCR reaction was subjected to initial denaturation at 94°C for 10 min., and 35 cycles of each of 1 min at 94°C, 1 min., at 63°C and 1 min at 72°C followed by final extension at 72°C for 30 mins. The fragments were analyzed on a 1.2 % agarose gel and stained with ethidium bromide.

Page No: 18



Nested PCR: DNA extracted from clinical samples / cultivated mycobacterial were processed for PCR with primers Seq.ID. No.1-N and Seq.ID. No.2-S. The PCR product obtained using the primers Seq.ID. No.1-N and Seq.ID. No.2-S was used as target DNA in nested PCR.

Each reaction (40μl) contained 2.5 mM MgCl₂, 0.5 μM of primers, 200 μM dNTPs, 10 mM Tris-HCl (pH 8.8 at 25°C), 50 mM KCl, 0.08% Nonidet P40, and 0.5 Units of Taq DNA Polymerase. The PCR reaction was subjected to initial denaturation at 95°C for 10 min., and 35 cycles of 1 min at 94°C, 1 min., and 30 seconds at 59°C and final extension at 72°C for 7 mins. The fragments were analyzed on a 3.5 % agarose gel / 8 % non-reducing polyacrylamide gel and stained with ethidium bromide. The C- terminal portion of the gene was also amplified by using Seq.ID. No.4-F (5' ccaagaaggcgacaaagg3') with Seq.ID. No.5-R (5' gacagctttcttggcggg3'), the expected amplicon was ~ 116 bp in case of *M.tuberculosis* and 89 bp in case of *M.bovis*, (Table II, Fig.1).

Southern Hybridization: The PCR amplicons resolved on the agarose gel were transferred on to nitro-cellulose membrane (Southern, 1975). The blots were then hybridized with α-32P labeled 645 bp hupB (Seq ID No.6) gene probe from M. tuberculosis, (Pstl & Ncol digest from the plasmid pHLPMT, / probe generated by PCR using N (Seq ID No.1-N) and S (Seq ID No.2-S) primers and M. tuberculosis, DNA.).

Restriction Fragment Length Polymorphism:

Page No.: 25

, Sequence

<213> OrganismName : Mycobacteria

<400> PreSequenceString : VKPTSVPAFR PGAQFK

16

<212> Type : PRT <211> Length : 16

SequenceName: seq id no. 6 (Change to 8)

SequenceDescription:

. Sequence

<213> OrganismName: hup B - M. tuberculosis, Rv2986c, Accession No. P95109
<400> PreSequenceString:

atgaacaaag cagagctcat tgacgtgctc acacagaaat tgggctcgga ccgtcggcag 60 gcgaccgccg ccgtcgagaa tgtcgttgac acgattgtgc gtgcggtaca caaaggcgac 120 agegteacea ttacegggtt eggtgtgtte gaacagegte geegeggge tegagtggee 180 cgcaatccgc gtaccggcga gacagtaaag gtgaagccga cgtcggtgcc ggcgttccgc 240 ccgggcgcgc aattcaaagc ggttgtgtct ggcgcgcagc gtctcccggc agaaggaccc 300 gctgttaagc gtggtgtggg ggccagtgca gccaagaagg tagcgaagaa ggcacctgcc 360 aagaaggega caaaggeege caagaaggeg gegaccaagg egeeegeeag gaaggeggeg 420 accaaggege cegecaagaa ageggegaee aaggegeeeg ceaagaaage tgteaaggee 480 acgaagtcac ccgccaagaa ggtgaccaag gcggtgaaga agaccgcggt caaggcatcg 540 gtgcgtaagg cggcgaccaa ggcgccggca aagaaggcag cggccaagcg gccggctacc 600 aaggeteeeg eeaagaagge aacegetegg eggggtegea aatag 645

<212> Type: DNA <211> Length: 645

SequenceName: Seq id no.7 (Change to 6)

SequenceDescription:

Sequence

<213> OrganismName: Hlp of Mycobacterium bovis, Acession No. Y18421 <400> PreSequenceString: atgaacaaag cagagctcat tgacgtgctc acacagaaat tgggctcgga ccgtcggcag 60 gcgaccgccg ccgtcgagaa tgtcgttgac acgattgtgc gtgcggtaca caaaggcgac 120 agegteacea ttacegggtt eggtgtgtte gaaeagegte geegegege tegagtggee 180 cgcaatccgc gtaccggcga gacagtaaag gtgaagccga cgtcggtgcc ggcgttccgc 240 ccgggcgcgc aattcaaagc ggttgtgtct ggcgcgcagc gtctcccggc agaaggaccc 300 gctgttaagc gtggtgtggg ggccagtgca gccaagaagg tagcgaagaa ggcacctgcc 360 420 accaaggege cegecaagaa agetgteaag gecaegaagt caeeegeeaa gaaggtgaee 480 aaggeggtga agaagacege ggteaaggea teggtgegta aggeggegae caaggegeeg 540 gcaaagaagg cagcggccaa gcggccggct accaaggctc ccgccaagaa ggcaaccgct 600 cggcggggtc gcaaatag 618

<212> Type: DNA <211> Length: 618

SequenceName: Seq id no.8 (Change to 7)

SequenceDescription:

Sequence

<213> OrganismName: 23S- Genus Mycoabcteria-C <400> PreSequenceString: gtgagcgacg ggatttgcct at 22 <212> Type: DNA <211> Length: 22 SequenceName: seq id no. 9

SequenceName: seq id no. 9 SequenceDescription:

Sequence

<213> OrganismName : 23S-Genus Mycobacteria-L
<400> PreSequenceString :
accacccaaa accggatcga t
<212> Type : DNA
<211> Length : 21

SequenceName: Seq id no. 10 SequenceDescription:

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

BLACK BORDERS

IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

FADED TEXT OR DRAWING

BLURRED OR ILLEGIBLE TEXT OR DRAWING

SKEWED/SLANTED IMAGES

COLOR OR BLACK AND WHITE PHOTOGRAPHS

GRAY SCALE DOCUMENTS

LINES OR MARKS ON ORIGINAL DOCUMENT

REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

IMAGES ARE BEST AVAILABLE COPY.

☐ OTHER:

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.